

## RESEARCH OUTPUTS / RÉSULTATS DE RECHERCHE

### Patients on a Fixed Dose of DOAC

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and ticagrelor. The concomitant use of edoxaban and antiplatelet agents exerted the combination effects. These results suggest that edoxaban alone and in combination therapies with edoxaban plus aspirin and edoxaban plus clopidogrel are promising options for prevention of stent thrombosis.

## PB 1234 | Dental Extractions on NOACs without Stopping Therapy (DENTST) Study: Interim Analysis

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**Background:** International guidelines recommend warfarin be continued for dental extractions, as bleeding rates are not high; instead, discontinuation can result in venous thromboembolism (VTE). There is currently no published data from clinical trials to guide the management of patients on new oral anticoagulants (NOACs) requiring dental intervention.

**Aims:** To determine the safety of performing dental extractions on patients taking NOACs. Secondary aims are to identify factors associated with increased bleeding risk and to determine if there is a safe lower limit of NOAC drug level below which dental extractions may be safely performed.

**Methods:** This is a prospective cohort study with 3 groups: patients on NOAC, warfarin, or no anticoagulant. The study has local ethics approval and informed consent is obtained. Participants do not withhold their anticoagulant. Blood tests are measured immediately prior to extraction. After extraction, Surgicel is placed in the socket, the socket then sutured and pressure applied with gauze. The gauze is weighed before and after haemostasis is achieved, and blood loss estimated by laboratory analysis. Bleeding complications are assessed at 48 hours and 7 days.

**Results:** Recruitment commenced in February 2016 with a target completion of November 2018. Data from 41 participants available

at the time of abstract submission is summarised in tables 1 and 2. There have been 2 episodes of clinically relevant non-major bleeding: both were delayed bleeding requiring unanticipated dental review in patients on warfarin with therapeutic INRs. The difference in weight of gauze appears to indicate that patients on NOACs bleed less than warfarin. Interim blood loss analysis suggests this is typically low and not clinically significant.

**TABLE 2** Anticoagulant drug levels

Oral anticoagulant	Warfarin	Apixaban	Dabigatran	Rivaroxaban
Assay	INR	Anti-Xa	Dilute thrombin time	Anti-Xa
Median drug level (range)	2.2 (2.0-2.4)	136.1 ng/ml (37.3-238.7)	122.3 ng/ml (68.5-188.1)	137.0 ng/ml (11.0-487.0)

**Conclusions:** Interim results suggest that bleeding outcomes in patients on NOACs are comparable and perhaps less than patients on warfarin. NOAC interruption may be unnecessary for dental extractions.

## PB 1235 | Patients on a Fixed Dose of DOAC: What Percentage is in the Therapeutic Window?

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**Background:** Adequate antithrombotic medication ideally modulates the function of the clotting system to a certain therapeutic window (TW) to minimize thrombotic recurrence while maintaining adequate hemostasis, i.e. prevent bleeding. For anti-vitamin K (AVK) treatment

**TABLE 1** Patient details and outcomes

Oral anticoagulant	Warfarin	All NOACs	Apixaban	Dabigatran	Rivaroxaban	No anticoagulant
Patient number	6	22	12	4	6	13
Total number of teeth extracted	10	48	17	15	16	27
Total number of roots extracted	15	67	27	18	22	48
Any bleeding	3 (50%)	5 (23%)	3 (25%)	1 (25%)	1 (17%)	1 (8%)
Major bleeding episodes	0	0	0	0	0	0
Clinically relevant non-major bleeding episodes	2 (33%)	0	0	0	0	0
Minor bleeding episodes	1 (17%)	5 (23%)	3 (25%)	1 (25%)	1 (17%)	1 (8%)
Difference in weight of gauze per tooth (grams)	3.24	2.00	2.91	1.80	1.29	1.82
Difference in weight of gauze per root (grams)	2.16	1.42	1.83	1.50	0.94	1.03

the TW is roughly an international normalized ratio (INR) of 2-4. For heparins and direct oral anticoagulants (DOACs), the TW is unknown. Therefore, their dosage can only be based on the outcome of clinical trials using standard dosages.

Ample evidence exists that the thrombin generating capacity (TGC) of plasma, measured as the area under the thrombin generation curve (Endogenous Thrombin Potential, ETP) is an adequate surrogate parameter for both thrombotic- and bleeding tendency. An INR of 2-4 corresponds to a TGC of 33-66% of the normal mean, and TGC < 30% is the clinical limit of a bleeding phenotype in congenital bleeding disorders. We therefore assume 66%>TGC>33% as a tentative TW for all anticoagulant treatment.

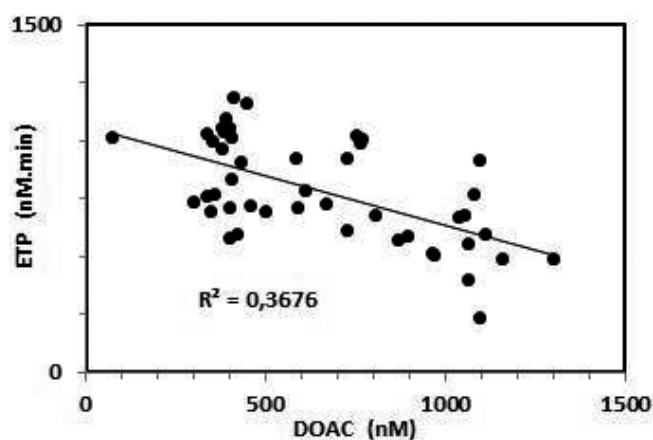
**Aims:** To estimate the amount of patients on DOACs within the TW.

**Methods:** Plasmas from 60 healthy volunteers were spiked with low molecular weight heparin (LMWH), unfractionated heparin (UFH) or DOACs at concentrations that inhibit TGC in pooled normal plasma by 40%. In plasma of 48 patients on rivaroxaban samples were harvested 2±0.6 h after intake. The concentration of the drug was measured by its inhibition of factor Xa activity and the ETP was assessed by Calibrated Automated Thrombinography.

**Results:** The individual response of normal plasmas to an IC40 concentration of heparin and DOACs proved to be highly variable (Table).

**TABLE 1**

	Normal plasma	N	CV (%)	Above TW	Below TW
Spiked Plasma	None	60	18.0	99	0
	UFH	60	27.8	14	9
	LMWH	50	29.0	15	10
	DOAC-IIa	40	23.9	10	6
	DOAC-Xa	40	21.5	10	5
Patient Samples	DOAC-Xa	22	27.0	14	9



**FIGURE 1**

The level of the direct anti-Xa inhibitor measured in patient samples had a CV of 46% and a poor correlation was found between inhibition of ETP and the DOAC levels (Fig. 1).

**Conclusions:** Inter-individual variation of both pharmacokinetics and pharmacodynamics of the tested DOACs is so high that maintenance within the TW is only possible by personalized dosage guided by the effect of the drug on the TGC.

## PB 1236 | Comparing the Performance of Different Assays for Monitoring Dabigatran Plasma Concentrations in Real-practice

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**Background:** Patients under therapeutic doses of dabigatran, a direct thrombin inhibitor, do not require routine coagulation monitoring. However, it may be important in certain clinical situations to assess anticoagulant activity. Most guidelines recommend to perform activated partial thromboplastin time (APTT) and thrombin time as screening assays, and dilute thrombin time (dTT) or ecarin chromogenic assays (ECA) to determine dabigatran plasma concentration.

**Aims:** Compare the results obtained with ECA, used in our laboratory, and two dTT assays, and correlate ECA with APTT. This will enable us to choose the best test for our hospital.

**Methods:** Blood samples were collected from 18 patients taking therapeutic doses of dabigatran, admitted to our emergency room. Plasma dabigatran concentrations were determined with STA®-ECA II (Diagnostica Stago) and compared with 2 methods of dilute thrombin time: Hemoclot® Thrombin Inhibitor (Hyphen Biomed) and a dilute thrombin time assay based on STA®-Thrombin. APTT was determined with Pathromtin® SL (Siemens). All tests were performed on STA-R® Max coagulation analyser (Diagnostica Stago).

**Results:** ECA showed high correlation with dTT assays, across a broad range of dabigatran levels. The correlation between ECA and Hemoclot® was very strong ( $R=0,980$ ;  $R^2=0,960$ ), as well as between ECA and dTT based on STA®-Thrombin ( $R=0,994$ ;  $R^2=0,987$ ). Both dTT assays values were similar, with excellent correlation ( $R=0,994$ ;  $R^2=0,989$ ). The correlation between ECA and APPT was strong ( $R=0,814$ ;  $R^2=0,663$ ). ECA showed to be more sensitive and useful for detecting very low dabigatran levels (limit detection level: 15 ng/ml) than dTT assays (limit detection level: 50 ng/ml).

**Conclusions:** This study showed that dTT and ECA accurately identify a broad range of dabigatran levels. The lower limit detected by ECA is 15 ng/ml, which can be important for patient needing high-risk surgery. Facing these results we decide to maintain ECA as the quantitative test for dabigatran in our hospital.